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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/009,473 | 11/08/2001 | Michael Hagen | 33,482-00 | 3152 |

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| EXAMINER | |
|---|---|
| LE, EMILY M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/009,473 | HAGEN, MICHAEL | |
| | Examiner | Art Unit | |
| | Emily Le | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04/06/2006 and 07/31/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-90,98,105,109,116-119,160,163,164 and 167* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/23/06 +04/06/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 88-90, 98-119, 127-130, 138-141, 149-152, 160, 162-164, 166-168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185-199.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 99-104, 106-108, 110-115, 127-130, 138-141, 149-152, 162, 166, 168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185-199.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/06/2006 has been entered.

### *Election/Restrictions*

2. Applicant's election without traverse of Group I, the adjuvant combination of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and granulocyte macrophage colony stimulating factor (GM-CSF), in the reply filed on 7/31/2006 is acknowledged.

### *Status of claims*

3. Claims 1-87, 91-97, 120-126, 131-137, 142-148, 153-159, 161, 165, 169, 172, 175, 178, 181 and 184 are cancelled. Claims 186-199 are added. Claims 88-90, 98-119, 127-130, 138-141, 149-152, 160, 162-164, 166-168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185-199 are pending. Claims 99-104, 106-108, 110-115, 127-130, 138-141, 149-152, 162, 166, 168, 170-171, 173-174, 176-177, 179-180, 182-183 and 185 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/21/2004 and 01/28/05.

Additionally, claims 186-199 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 07/31/2006. Claims 88-90, 98, 105, 109, 116-119, 160, 163-164 and 167 are under examination.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 88-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulrich et al. [1] and Disis et al.[2]

The claims are directed to a composition consisting of an antigen and an adjuvant, wherein the adjuvant consists of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and granulocyte-macrophage colony stimulating factor (GM-CSF), together with a diluent or carrier. Claim 89, which depends on claim 88, requires the antigen to be a peptide or protein. Claim 90, which depends on claim 88, requires

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[1] Ulrich et al. Monophosphoryl lipid A as an adjuvant. Past experiences and new directions. In M.F. Powell and M.J. Newman (ed.), Vaccine Design. Plenum Press, New York, NY, p. 495-523.
[2] Disis et al. Granulocyte-macrophage colony-stimulating factor: an effective adjuvant for protein and peptide based vaccines. Blood, 1996; Vol. 88, no. 1: 202-210.

3-O-deacylated monophosphoryl lipid A be used in the form of a stable oil-in-water emulsion.

Ulrich et al. teaches the use of monophosphoryl lipid A as an adjuvant to bacterial and viral protein and peptide based vaccines to enhance antibody response to said bacterial and viral protein or peptide. [Pages 509-513, in particular.] Ulrich et al. also teaches the inclusion of the adjuvant with a carrier. [Section 3.2.1, page 503, in particular.] Specifically, Ulrich et al. teaches the presentation of monophosphoryl lipid A in a stable oil-in-water emulsion. In summary, Ulrich et al. teaches that MPL alone or in combination of other vehicles or immunomodulators provides the appropriate adjuvant activities for a variety of vaccine antigens, including protein and peptide antigens.

However, Ulrich et al. does not teach the inclusion of granulocyte-macrophage colony stimulating factor (GM-CSF).

Disis et al. teaches the use of granulocyte-macrophage colony stimulating factor (GM-CSF) as a potent adjuvant for the generation of immune responses, both humoral and cell-mediated, to foreign proteins as well as peptide-based vaccines. [Abstract, in particular.]

In the instant, both monophosphoryl lipid A and granulocyte-macrophage colony stimulating factor (GM-CSF) are art recognized adjuvants. Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine two art-recognized adjuvants into one composition. [See *In re* Kerkhoven and MPEP § 2144.06 [R-3].] One of ordinary skill in the art at the time the invention was made would have been motivated to do so to enhance the immune

response against an antigen of interest. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the adjuvant activity of both monophosphoryl lipid A and GM-CSF is well recognized in the art at the time the invention was made. Therefore, the claimed invention is obvious over the teachings both Ulrich et al. and Disis et al.

7. Claims 88, 98 and 116-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulrich et al. and Disis et al., as applied to claim 88, in view of Bartlett et al.[3]

Claim 98, which depends on claim 88, requires the antigen to be derived from a pathogenic virus. Claim 116, which depends on claim 98, requires the pathogenic virus is human immunodeficiency virus, HIV. Claim 117, which depends on claim 116, requires the HIV antigen be a protein, polypeptide or peptide. Claim 118, which depends on claim 117, further limits the HIV antigen to those having the amino acid sequence set forth in SEQ ID NO: 2. Additionally, claim 119, which depends on claim 116, requires 3-O-deacylated monophosphoryl lipid A to be in the form of a stable oil-in-water emulsion.

The significance of Ulrich et al. and Disis et al., as applied to claim 88, is discussed above. In the instant, neither Ulrich et al. nor Disis et al. teaches an HIV antigen having the amino acid sequence set forth in SEQ ID NO: 2. However, the deficiency noted in Ulrich et al. and Disis et al. is fully compensated by the teachings of Bartlett et al. Bartlett et al. teaches C4-$V3_{MN}$, which has the following sequence:

KQIINMWQEVGKAMYATRPNYNKRKRIHIGPGRAFYTTK. [Immunogen design, peptide synthesis and purification section, page 1292, in particular.] In the instant, the C4-$V3_{MN}$ peptide that Bartlett et al. teaches has the same amino acid sequence as SEQ ID NO: 2, which has the following amino acid sequence: KQIINMWQEVGKAMYATRPNYNKRKRIHIGPGRAFYTTK. Bartlett et al. teaches the use of C4-$V3_{MN}$ to elicit an HIV-antigen specific immune response. Hence, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the adjuvant composition of Ulrich et al. and Disis et al. with the HIV antigen of Bartlett et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to enhance the immunogenicity of the HIV antigen that Bartlett et al. teaches. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of adjuvant to enhance the immunogenicity of antigens is routinely practiced in the art. Furthermore, the adjuvanting effects of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and GM-CSF, together with a carrier or a diluent has been recognized in the art at the time the invention was made. Therefore, the claimed invention is obvious over the teachings of Ulrich et al., Disis et al. and Bartlett et al.

8. Claims 88, 98, 105, 109, 116, 160, 163-164 and 167 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulrich et al. and Disis et al., in view of Bartlett et al., as applied to claims 88, 98 and 116.

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[3] Bartlett et al. Safety and immunogenicity of an HLA-based HIV envelope polyvalent synthetic peptide

Claims 105, 109, 160, 163-164 and 167 are directed to the administration of the composition of claims 98 (as it pertains to claims 105 and 109) and 116 (as it pertains to claims 160, 163-164 and 167) to elicit an immune response in a subject. In the instant, claim 105 and 109 recite a direct dependency to claim 98, which depends on claim 88; and claims 160 and 164 recite a direct dependency to claim 116, which depends on claim 98. Additionally, claim 163 recites a dependency to claim 160; and claim 167 recites a dependency to claim 164. In addition to eliciting an immune response in the subject, claims 109 and 164 requires that the immune response be a CTL response. Lastly, claims 163 and 167 require the antigen administered to have the amino acid sequence set forth in SEQ ID NO: 2.

The significance of Ulrich et al., Disis et al. and Bartlett et al., as applied to claims 88, 98 and 116, is discussed above. In the instant, Ulrich et al., Disis et al. and Bartlett et al. do not teach the administration of the composition of claims 98 and 116; however, as discussed above, the antigen of Bartlett et al. is a multideterminant peptide comprising T-helper epitopes from the fourth constant region (C4) of gp120 of HIV-$1_{MN}$, and T-helper, and cytotoxic T-lymphocyte HLA-B7-restricted; and B-cell neutralizing epitopes from the gp120 third variable region. Bartlett et al. teaches the administration of the multideterminant peptide to induce an HIV specific immune response. Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to administer the HIV antigen of Bartlett et al. with the adjuvant composition that Ulrich et al. and Disis et al. teaches. One of ordinary skill in the art at

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immunogen. AIDS, 1998, Vol. 12, No. 11, 1291-1300.

the time the invention was made would have been motivated to do so to enhance the immunogenicity of the HIV antigen that Bartlett et al. teaches. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of adjuvant to enhance the immunogenicity of antigens is routinely practiced in the art. Furthermore, the adjuvanting effects of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and GM-CSF, together with a carrier or a diluent has been recognized in the art at the time the invention was made. Therefore, the claimed invention is obvious over the teachings of Ulrich et al., Disis et al. and Bartlett et al.

Additionally, the administration of the antigen of Bartlett et al. would necessarily induce a CTL response in the subject. As noted above, the antigen of Bartlett et al. contains CTL specific epitopes. Thus, the administration of said antigen would necessarily induce a CTL response in the subject.

***Conclusion***

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Emily Le 10/22/06
Patent Examiner
Art Unit 1648